REACh – How does it affect the pharmaceutical industry?

Consideration of the issue for a medium-sized enterprise.

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List of abbreviations

BAUA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
BAH	Bundesverband der Arzneimittelhersteller e.V.
CA	Competent Authorities (of the Member States)
CAS	Chemical Abstracts Service
CM	Contract Manufacturer
CMR	Carcinogen, mutagen, reproductive toxic (substances)
CRO	Contract Research Organisation
EC	European Community
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
ESIS	European chemical Substances Information System
EU	European Union
FELS	Fish early-life stage
GLP	Good Laboratory Practice
INN	International Nonproprietary Name
IUCLID	International Uniform Chemical Information Database
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder (of a medicinal product)
MS	Member State(s)
MSC	Member States Committee
MSDS	Material Safety Data Sheet
p.a.	Per year (per annum)
PBT	Persistent, bioaccumulative, toxic (substances)
PPM	Primary Packaging Material
PPORD	Product and process oriented research and development
QSAR	Quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIP	REACH Implementation Project
SIEF	Substance Information Exchange Forum
SME	Small and medium sized enterprises
SR&D	Scientific Research and Development
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials
vPvB	Very persistent, very bioaccumulative (substances)

1. How did it start? – A short introduction

In 1957 the European Community was created with the objective to protect the rights and interests of the citizens of the Member States and to establish a region with free trade and transport of goods [Lit 1]. Both objectives should be accomplished e.g. by harmonisation of the laws in the different Member States. So, in order to concern health, safety and the protection of man and the environment and to create open competition for chemicals, the political institutions were decided to harmonize the chemical laws in the EU.

Many directives and regulations are passed to govern certain topics, e.g. Council Directive 76/769/EEC, which deals with the use of “certain dangerous substances and preparations” (polychlorinated biphenyls, polychlorinated terphenyls, vinyl chloride) [Lit 2], or Commission Directive 91/155/EEC, which defines standards for material safety data sheets of dangerous substances and preparations [Lit 3].

Additionally two general approaches to regulate the movement of chemicals within the EC by law took place in 1981 and 1993. Both efforts resulted in a division of chemicals into two classes: one class comprising approximately 97 % (= 100.000) of substances, for which nearly no data on risk for human health and the environment were available, and another class (3 %, 4.000) of substances, which were evaluated regarding their risks [Lit 4, Lit 5]. Both laws will be summarised in subchapters 1.1 and 1.2. of this thesis.

These laws did not succeed in a harmonisation of standards for all chemicals marketed in the EU, therefore a further reform of the chemicals legislation was required. Accordingly, at June 1st 2007 the third approach, regulation (EC) No 1907/2006, so called REACH regulation, came into force [Lit 10]. REACH means **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals. The regulation stands for a complete revision of the European chemicals legislation and overrules or modifies many directives and regulations concerning chemical substances and chemical preparations. The main contents of this regulation concerning the topic of this thesis are presented in chapter 2. A pre-registration procedure, which allows the registrant to take the statutory transition periods, is described as well as the registration procedure including e.g. the collection of data, the submission of documentation and the completeness check at the European Chemicals Agency. Additionally the evaluation of substances and the authorisation of dangerous substances are introduced.

To support the responsible persons concerned, Guidance Documents regarding different problems, e.g. how to prepare a registration dossier, how to deal with intermediates or polymers, are developed during REACH Implementation Projects. The contents of the guidances available will be summarised in subchapter 2.5.

But how is the pharmaceutical industry affected by REACH? Human and veterinary medicinal products are exempted from the regulation and therefore the pharmaceutical industry seems not to be involved. Using a few examples it will be demonstrated in chapter 3, that the circumstances are more complex than it seems at first sight and that the consequences could be serious also for the marketing authorisations of medicinal products. Using the example of a

medium-sized enterprise without its own production facilities an approach for dealing with the REACH regulation and for guarantee of the further availability of substances is made in Chapter 4. Here the different steps necessary during the pre-registration and the registration phase of a substance are described in detail.

1.1 Council Directive 67/548/EEC

Council Directive 67/548/EEC [Lit 6], which was supposed to be transferred into national law at January 1st 1970, was the first directive focussed to approximate the legislation on classification, packaging and labelling of dangerous substances in the member states of the EU. It was adapted thirty times and amended ten times until now to take into account scientific and technical progress. The primary version of the directive was confined to define general standards for packaging and labelling of dangerous substances. Dangerous preparations were excluded from the directive. An extensive revision took place with Council Directive 92/32/EEC [Lit 7], which amended Council Directive 67/548/EEC for the 7th time. The directive, which was meant to come into force by the member states till October 31st 1993, introduced an obligatory registration for each new chemical substance before first placement on the market. The registration is not limited to dangerous substances or substances exceeding a defined yearly amount, but the extent of documentation depends on the quantity marketed. Each substance registered has to undergo a risk assessment by the national competent authority. The development on the market and the use of the new chemical substances is observed closely by the competent authority, too. Excluded from the directive are e.g. medicinal products, cosmetic products, food and chemical substances already marketed since September 18th 1981. The latter are listed in the index EINECS (= European Inventory of Existing Commercial Chemical Substances) and they are called “phase-in substances” in terms of the REACH regulation.
Substances, which are registered according to Council Directive 67/548/EEC as amended are listed in ELINCS, which stands for European List of Notified Chemical Substances.

1.2 Council Regulation (EEC) No 793/93

In June 1993 Council Regulation (EEC) No 793/93 [Lit 8] got into force. Scope of this regulation is a systematic risk assessment of chemical substances, which are marketed since September 18th 1981 and listed in EINECS. These substances are excluded from Council Directive 67/548/EEC and are therefore not subject of the control mechanisms mentioned in the directive [see also subchapter 1.1].
The risk of EINECS substances is evaluated preliminary to identify high risk substances. The latter are reviewed preferentially by the national competent authorities. For these purposes each manufacturer and importer has to submit data regarding the physico-chemical characteristics and the toxicity, whereas the extent of data depends on the yearly amount of the substance synthesized or imported. If toxicity data are not available and additional animal studies are required, remarkably, the manufacturer or importer is not bound to carry out such studies.
With Regulation (EC) No 1907/2006 coming into force on June 1st 2007 Council Regulation (EEC) No 793/93 was repealed [see also chapter 2].

2. What is the REACH regulation about? - Scope and contents

2.1 Survey of Regulation (EC) No 1907/2006

As well as the above mentioned Council Directive 67/548/EEC and Council Regulation (EEC) No 793/93 Regulation (EC) No 1907/2006 [Lit 10], so called REACH regulation, has the aim to protect human health and environment and to guarantee free movement of chemicals within the EU. The differentiation between the two classes of chemicals, which had been arisen from the former legislation [see also chapter 1], will be annulled stepwise till 2018 [Lit 4]. The time schedule is presented in Fig. 1.

Fig. 1 Time schedule presenting the different stages of Regulation (EC) No 1907/2006

"Pre-pre-registration period"	01.06.2007	Regulation (EC) No 1907/2006 came into force
Pre-registration period	01.06.2008	Start of the pre-registration period
	01.12.2008	End of the pre-registration period
Registration period	01.01.2009	Publication of a list of pre-registered substances
	01.12.2010	Deadline for submission of registration dossiers for substances of ≥ 1000 tons p.a. and of dangerous substances as mentioned in Tab. 2
	01.06.2013	Deadline for submission of registration dossiers for substances of ≥ 100 tons p.a.
	01.06.2018	Deadline for submission of registration dossiers for substances of ≥ 1 ton p.a.

In contrast to the former legislation the REACH-regulation covers not only chemical substances but also chemical preparations and articles. The latter are defined in article 3 of the regulation as follows. A preparation is a mixture or solution composed of two or more substances whereas an article means an object, whose appearance determines its function more than its chemical composition. But it has to be pointed out, that the obligations of the regulation are limited to chemical *substances* on their own, in preparations or in articles.
Additionally substances used for scientific research and development and so called UVCB substances (= substances of unknown or variable composition, complex reaction products or biological materials) are taken into account.

Excluded from the regulation are substances used in e.g. medicinal products and in food or feeding stuff regarding the registration procedure as well as preparations in the finished state e.g. medicinal products, cosmetics, medical devices and food and feeding stuff regarding the transmission of information.

A very important aspect of the regulation is the shifting of the burden of the proof. Now the manufacturer or importer has to provide the data necessary for evaluation of his substances, whereas in the former legislation the competent authorities had to detect the risks on their own. Each manufacturer and importer has to register his

substances, if the yearly amount imported or manufactured exceeds one ton, and to submit a dossier, whose extent depends on the yearly amount of production. The following tonnage thresholds are mentioned in the regulation: ≥ 1 ton p.a., ≥ 10 tons p.a., ≥ 100 tons p.a. and ≥ 1000 tons p.a. The dossier will be checked by an agency [see also below] of completeness. Additionally a certain percentage of dossiers will be checked for compliance. Moreover dangerous substances have to be authorised by the agency. A more detailed description of the (pre-) registration procedure can be found in subchapter 2.2. Subchapters 2.3 and 2.4 will be dwelling on the evaluation of dossiers and the authorisation of substances of high concern.

However substances, which are notified according to Council Directive 67/548/EEC, are regarded as registered and should be transferred into the system based on the REACH regulation when the next quantity threshold is reached. But it has to be considered, that the registration is just valid for the manufacturer or importer, who notified the substance. Any other manufacturer or importer, who wants to place the same substance on the market for the first time, has to pass the registration procedure [Lit 9].

In contrast to Council Regulation (EEC) No 793/93, where is says, that each manufacturer or importer has to submit the information required on his own, the REACH regulation commits all manufacturers and importers, who pre-registered for a certain substance, to work together in a so called SIEF (= Substance Information Exchange Forum) and to share the information on substances for reduction of costs and testing on vertebrate animals. The topic will be discussed in subchapter 2.2.

For carrying out the technical, scientific and administrative aspects the regulation established the European Chemicals Agency (= ECHA).

An important objective of the regulation is the replacement of dangerous substances with substances of less concern or with technologies, which are economically and technically viable.

The regulation also gives emphasis on the transfer of information in the supply chain as well as to the public. It commits manufacturers and importers to inform downstream users whether a substance will be registered or not. Additionally both have to undertake safety assessment of their substances regarding their own and their customers' uses. For successful risk management of the substances manufacturers and importers as well as downstream users or distributors have to inform each other on (newly arising) risks and the safe use of the chemicals. The downstream user, which is newly introduced with the REACH regulation, is defined as a person, who uses a substance either as its own or in a preparation in the course of his industrial or professional activities. Distributors or consumers are not numbered among downstream user.
The pubic should be informed on substances via a database of the ECHA, which gives free and easy access to basic data. It should allow the citizens to make informed decisions about their use of the substances.

2.2 Pre-Registration and Registration of Substances

2.2.1 Pre-Registration of Substances

The pre-registration of substances is fixed in article 28 of Regulation (EC) No 1907/2006. It is mandatory for substances produced or imported in quantities of one ton or more per year, for which the transition periods for registration [see also subchapter 2.2.4] should be taken. To pre-registrate a substance the manufacturer or importer has to submit to the ECHA the name of the substance, the name and address of the contact person, the estimated deadline for registration and the tonnage band [see also subchapter 2.2.4]. Pre-registration is possible during a six-month period from June 1st 2008 to December 1st 2008.

For submission of data the software IUCLID 5 has to be used, which can be downloaded from the homepage of the ECHA for free [Link 1].

Till January 1st 2009 the ECHA will publish a list of pre-registered substances including the estimated deadline for registration. If a downstream user misses a substance, he has the possibility to notify his interest in this substance to the ECHA, who will publish the name of the substance on its website and will provide the contact details of the downstream user to a potential registrant.

If the quantity of one ton of substance manufactured or imported is reached after December 1st 2008, the manufacturer and/or the importer can still use the transitional periods, if the information required for pre-registration is submitted to the ECHA within six months after first manufacture or import and if the submission of information takes place at the latest twelve months till the end of transitional period of the appropriate tonnage band.

Manufacturers and importers of substances manufactured or imported in amounts less than one ton per year may also submit the information required for pre-registration, if they want to participate in the corresponding SIEF.

2.2.2 Obligation for Registration

In article 5 of the REACH regulation it is stated, that each chemical substance on its own, in a chemical preparation or in a chemical article has to be registered, if it fulfils the conditions mentioned as follows and if it should be manufactured or imported further on.
According to article 6 paragraph 1 of the regulation a registration application has be submitted to the ECHA, if the substance on its own or in a preparation is manufactured or imported in quantities of at least one ton per year.
The conditions for registration of chemical substances in articles are fixed in article 7 of the regulation. Here it says, that these substances have to be registered, if they are present in the article in quantities totalling over one ton per year and if they are intended to be released under normal or reasonably foreseeable conditions of use. The conditions are summarised in Tab. 1. Substances in articles, which are classified as carcinogen, mutagen or reproductive toxic (= CMR) or which are persistent, bioaccumulative and toxic (= PBT) or very persistent and very bioaccumulative (= vPvB), have to be notified to the ECHA, if they are present in the articles in quantities totalling over one ton per year and in concentrations of more than 0.1 % per mass and if an exposure to humans or environment during normal or reasonably

foreseeable conditions of use cannot be excluded. Then the ECHA can set up the submission of a registration dossier under regularized conditions.

As mentioned in article 17 of the regulation substances, which are used in plant protection products, as well as substances in biocidal products are regarded as registered, if they are listed in the annexes of the relating EU-legislation.

Tab. 1 Overview of conditions necessitating a registration

Chemical substance	Chemical substance in preparation	Chemical substance in article, non-CMR, non-PBT, non-vPvB	Chemical substance in article, CMR and/or PBT and/or vPvB
• Quantity manufactured or imported ≥ 1 ton p.a.	• Quantity contained in the preparation ≥ 1 ton p.a.	• Quantity contained in the article ≥ 1 ton p.a. • Intention to be released under normal or reasonably foreseeable conditions of use	• Quantity contained in the article ≥ 1 ton p.a. • Exposure to humans or environment during normal or reasonably foreseeable conditions of use cannot be excluded • Presence in the article > 0.1 % per mass

2.2.3 Registration Procedure

Submission of registration dossier

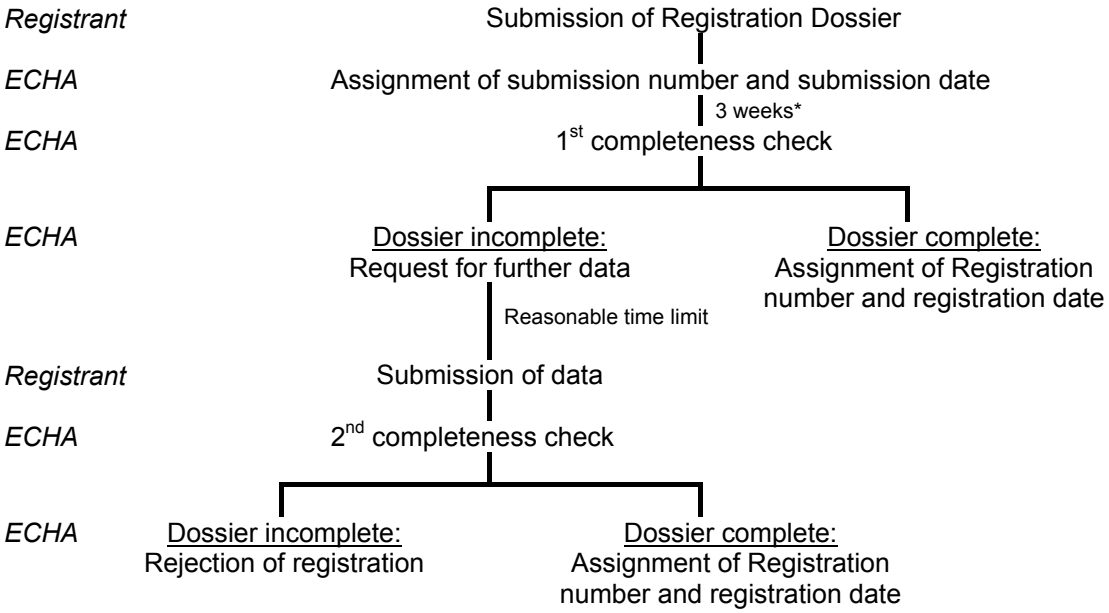
If a substance has to be registrated according to Regulation (EC) No 1907/2006 the manufacturer or importer established in the EU has to submit a registration dossier to the ECHA within the time limits fixed in the regulation [for timelines see also subchapter 2.2.4]. According to article 8 of the regulation manufacturers established outside the EU have to nominate one representative established in the EU, who has to fulfil the obligations of the REACH regulation. Without representative within the EU an export of substances or preparations or articles to EU countries isn't possible furthermore.

Examination of documentation by the ECHA

As fixed in article 20 of the regulation the *completeness* of the dossier is checked by the ECHA. Missing data have to be requested while setting a reasonable deadline. After submission of the data required the completeness check will be terminated. If, within three weeks after initial submission, the ECHA has not made a contrary notice, the applicant could start or continue manufacturing or importing based on article 21 of the regulation. An overview of the completeness check gives Fig. 2.

In a second step 5 % of the dossiers for each tonnage band will be checked for *compliance* with the requirements of the REACH regulation by the ECHA. Details of the compliance check are mentioned in subchapter 2.3.

Fig. 2 Overview of the Completeness Check of the Registration Dossier



* or within 3 months of the relevant deadline of article 23, if the dossier is submitted in the course of the two months period immediately proceeding the deadline

Post-registration activities

The duties of the registrant regarding the documentation after termination of registration are fixed in article 22 of the REACH regulation. He has to update the registration without undue delay, e.g. if the composition, the quantity manufactured or imported or the classification or labelling changed or if new uses or new risks have been identified. Each update of the dossier will be checked for completeness by the ECHA.

2.2.4 Time limits for Registration

The submission of a registration dossier is possible at each time point within the limits fixed in articles 23 and 24 of the regulation. These depend on the hazardousness of the substance and the quantity, which is manufactured or imported annually. An overview can be found in Tab. 2.

Tab. 2 Overview of the time limits depending on hazardousness of substance and quantity of annual manufacture and import

Quantity of annual manufacture or import of substance	Hazardousness of substance	Deadline for submission of registration dossier
≥ 1 ton p.a.		➔ 01.06.2018
≥ 100 tons p.a.		➔ 01.06.2013
≥ 1000 tons p.a.		➔ 01.12.2010
≥ 1 ton p.a.	+ CMR class 1 or 2	➔ 01.12.2010
≥ 100 tons p.a.	+ very toxic to aquatic organisms which may cause long term adverse effects in the aquatic environment (R50/53)	➔ 01.12.2010

Substances, which are notified according to Council Directive 67/548/EEC, are regarded as registrated and will get a registration number till December 1st 2008. If the annual amount of substance will reach the next tonnage threshold [see also subchapter 2.1], the requirements of Regulation (EC) No 1907/2006 for this tonnage threshold have to be fulfilled by the manufacturer or importer.

2.2.5 Documentation required for Registration

The registration dossier consists of two parts: a chemical safety report (if required) and a technical dossier including information about the physicochemical properties, the toxicology, the ecotoxicology, the manufacture and the identified uses as well as the classification and labelling of the substance.

Technical Documentation

The requirements for the technical documentation are laid down in articles 10 and 12 of Regulation (EC) No 1907/2006 whereas the extent of documentation is fixed in annexes VII till X of the regulation. It depends on the quantity of substance, which is manufactured or imported annually. Main differences pertain to the toxicological and ecotoxicological information, but there are also differences in the requirements regarding the physicochemical documentation. Annex 1, Annex 2 and Annex 3 of this thesis will resume these differences.

In annex VI of the regulation the general requirements for preparation of the dossier are laid down, whereas the conditions for deviations from the standard testing regime are mentioned in annex XI. An overview of the different tonnage bands and the related annexes gives Tab. 3.

However, according to the REACH regulation, any physicochemical, toxicological and ecotoxicological information that is available should be submitted to the ECHA. The required documentation should be treated as minimum requirement. If the quantity of a substance reaches the next tonnage threshold, the manufacturer or importer has to inform the ECHA about the additional information required.

Tab. 3 Overview of the different tonnage bands and related annexes of Regulation (EC) No 1907/2006

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Annexes				
Annex VI	X	X	X	X
Annex VII	X	X	X	X
Annex VIII		X	X	X
Annex IX			X	X
Annex X				X
Annex XI	X	X	X	X

Chemical Safety Report

In article 14 of the REACH regulation the conditions for the chemical safety report are fixed. The report is mandatory for substances manufactured or imported in quantities of 10 tons or more per year, which have to be registrated, and it covers the risks to human health and/or the environment arising from the intrinsic properties of the substance. For substances in preparations a submission is only omitted, if the substance is below a concentration limit defined in the regulation. The documentation

for dangerous substances has to be amended by exposure scenarios, an exposure assessment and a risk characterisation.

2.2.6 Acquisition of Information required for Registration

The test conditions described in annexes VII till X of the REACH regulation can be considered to be standard. The acquisition of data using other tests is possible, if the general rules set out in annex XI of the regulation are met. An omission of tests is possible, if this is justified through information on exposure and implemented risk management measures.

Generally animal tests on vertebrates should be replaced whenever possible by alternative methods e.g. in vitro methods or QSAR (= Quantitative structure-activity relationship) methods. Toxicological and ecotoxicological tests should be carried out in compliance with the principles of GLP (= Good Laboratory Practice), other international standards or methods should be recognised as equivalent by the ECHA in the forefront of realization. A continuous upgrade of the methods used is required.

If a substance is already registered, a new registrant could refer to the study summaries, if he can show, that the substance to be registered is the same as the substance already registered, especially also regarding the impurities.

2.2.7 Joint submission of Documentation for Registration

<u>General rules for data sharing</u>

When a substance is intended to be registered by more than one manufacturer and/or importer, the manufacturers and/or importers have to align with each other and to submit particular parts of the documentation together e.g. classification, labelling, study summaries. As also fixed in article 11 of the REACH regulation other information e.g. information about the identity of substance, about the manufacture and the use of the substance should be submitted separately. The documentation submitted has to comply with the requirements of the tonnage band concerned.
If there are several registrants for the same substance, a separate submission by a single registrant is only possible in the case, where the registrant can prove, that data sharing would be disproportionately costly for him or the joint submission would lead to disclosure of commercially sensitive data or when he disagrees with the lead registrant, who submits the joint data, on the selection of information.

The general rules for data sharing are laid down in articles 25 till 27 of Regulation (EC) No 1907/2006. E.g. it says that to limit duplication of tests and to avoid testing on vertebrates whenever possible, study summaries have to be shared by the manufacturers and/or importers. Furthermore summaries of studies, which were submitted at least twelve years ago, can be used for registration purposes by other manufacturers or importers. If the submission of data took place less than twelve years ago the potential registrant has to ask the previous registrant(s) for the information he requires. By the way the request is mandatory, when information regarding tests on vertebrates is needed. In other cases the request is optional. If the previous registrant agrees, the costs for the data collection will be shared between previous and potential registrant. In the case of failure of such an agreement the ECHA can permit the reference on the data if the potential registrant proofs, that he has paid his proportion of the costs.

Substance Information Exchange Forum

Manufacturers and importers, who pre-registrated a substance according to article 28 of the REACH regulation, are automatically participant of a so called SIEF (= Substance Information Exchange Forum) relating to the substance applied for. As mentioned in articles 29 and 30 of the regulation it is the aim of the SIEF to facilitate the exchange of information for purposes of registration as well as to harmonize classification and labelling of the particular substance. The participants should be provided with existing studies. Additionally, any need for further studies should be identified within the SIEF.
When a study on vertebrates is needed by one registrant, he has to inquire whether the relevant study is available within the SIEF. However, in cases of non-vertebrate studies this request is optional. A required study, which is not available, has to be conducted by one of the participants with allocation of costs and data between all participants. If the owner of a study on vertebrates refuses to share the data, the study should not be repeated. The denier couldn't register his substance, whereas the other members of the SIEF get the registration referring to the study for which approval was refused. Non-vertebrate studies, which are not provided on request, are regarded as "not available in the SIEF" and have therefore to be repeated.

2.2.8 Special Cases

Product and process oriented research and development (PPORD)

Article 9 of Regulation (EC) No 1907/2006 reflects the conditions for substances manufactured or imported for PPORD (= Product and process oriented research and development). These substances are exempted from registration for a period of five years, if their use is limited to PPORD. The manufacturer or importer only has to notify the substance to the ECHA, who has the possibility to impose conditions. The five years exemption period may be extended to a further maximum of five years or for substances developed for use in medicinal products or for substances, which are not placed on the market, to a further maximum of ten years, if it can be demonstrated, that the extension is justified [Lit 11].

On-site isolated and transported isolated intermediates

The conditions for registration of on-site isolated and transported isolated intermediates are laid down in articles 17 and 18 of the REACH regulation. If the quantity of the substance exceeds one ton per year, a registration dossier has to be submitted to the ECHA. The dossier consists of the available existing information concerning physicochemical, toxicological and ecotoxicological properties, a general description of use and details on risk management. Data from additional tests are not required. But it has to be assured, that the substances are only used under strictly controlled conditions and that the emission is minimised. If the before mentioned conditions are not fulfilled a full registration dossier has to be submitted [Lit 11].

Polymers

If a polymer should be manufactured or imported, the monomers and other substances contained in the polymer need to be registrated if they haven't already be registered and if the following conditions, listed in article 6 of the regulation, are fulfilled: the polymer consists of 2 % per mass or more of the chemically bound substance and the total quantity of the substance is one ton or more per year. It has to be taken into account, that though polymers themselves are exempted from

registration, they possibly have to be authorised, if the requirements for authorisation are fulfilled [Lit 12].

2.3 Evaluation of Substances

As mentioned in subchapter 2.2.3 a minimum of 5 % of *registration dossiers* for each tonnage band has to be evaluated by the ECHA. *Testing proposals* however, which are required for substances manufactured or imported in quantities of 100 tons or more, have to be examined without exception. Additionally based on the information of the registration dossier different *substances* have to be evaluated. An overview of the procedures will be given in subchapters 2.3.1, 2.3.2 and 2.3.3.
In general the registrant is obliged to submit information exceeding the documentation submitted for registration purposes on request of the ECHA and the competent authorities of the Member States. But if a registrant ceases the manufacture or import of a substance no further information will be requested except if there is potential long-term risk to human health or the environment. Moreover a registration will become invalid, if the manufacture or import is ceased upon receipt of a draft decision, which is mentioned in the following subchapters.

2.3.1 Evaluation of Testing Proposals

According to article 40 of the REACH regulation any testing proposal, which is part of a registration dossier or of a downstream user report providing information specified in annexes IX and X, has to be examined by the ECHA, whereas substances with CMR-, PBT- or vPvB-properties or dangerous substances, which are manufactured or imported in quantities over 100 tons per year and whose uses resulting in widespread and diffuse exposure, have to be worked on preferentially.
If testing on vertebrates is included in the testing proposal, this information will be published on the website of the ECHA for submission of scientifically valid information and studies from interested parties. The data submitted will be taken into account by the ECHA in preparing the decision.
The ECHA can decide to accept the testing proposal with or without modification. It can also reject the proposal or request additional tests. The information submitted by the manufacturer and/or importer will be evaluated and a further draft decision will be made, following the procedure described in subchapter 2.3.4.

For *non-phase-in* substances the ECHA has to prepare a draft decision within 180 days after receipt. The time limits for preparation of draft decisions for all *phase-in* substances are orientated on the deadlines for submission of registration dossiers and can be found in Tab. 4.

Tab. 4 Time limits for draft decisions on testing proposals for phase-in substances

Deadline for submission of registration dossier	Deadline for draft decisions on testing proposals
01.12.2010	01.12.2012
01.06.2013	01.06.2016
01.06.2018	01.06.2022

2.3.2 Evaluation of Dossiers

The evaluation of dossiers is described in articles 41 and 42 of Regulation (EC) No 1907/2006. At first the ECHA has to check, if the registration dossier submitted by the registrant complies with the requirements fixed in the related articles and

annexes of the regulation. Within twelve months of the start of compliance check a draft decision has to be prepared, in which the registrant is informed about further documentation, which has to be submitted within an adequate time limit. The submitted documentation will be checked, too and a draft decision will be made.
The decision making process is mentioned in articles 51 and 52 of the REACH regulation and will be described in subchapter 2.3.4.

2.3.3 Evaluation of Substances

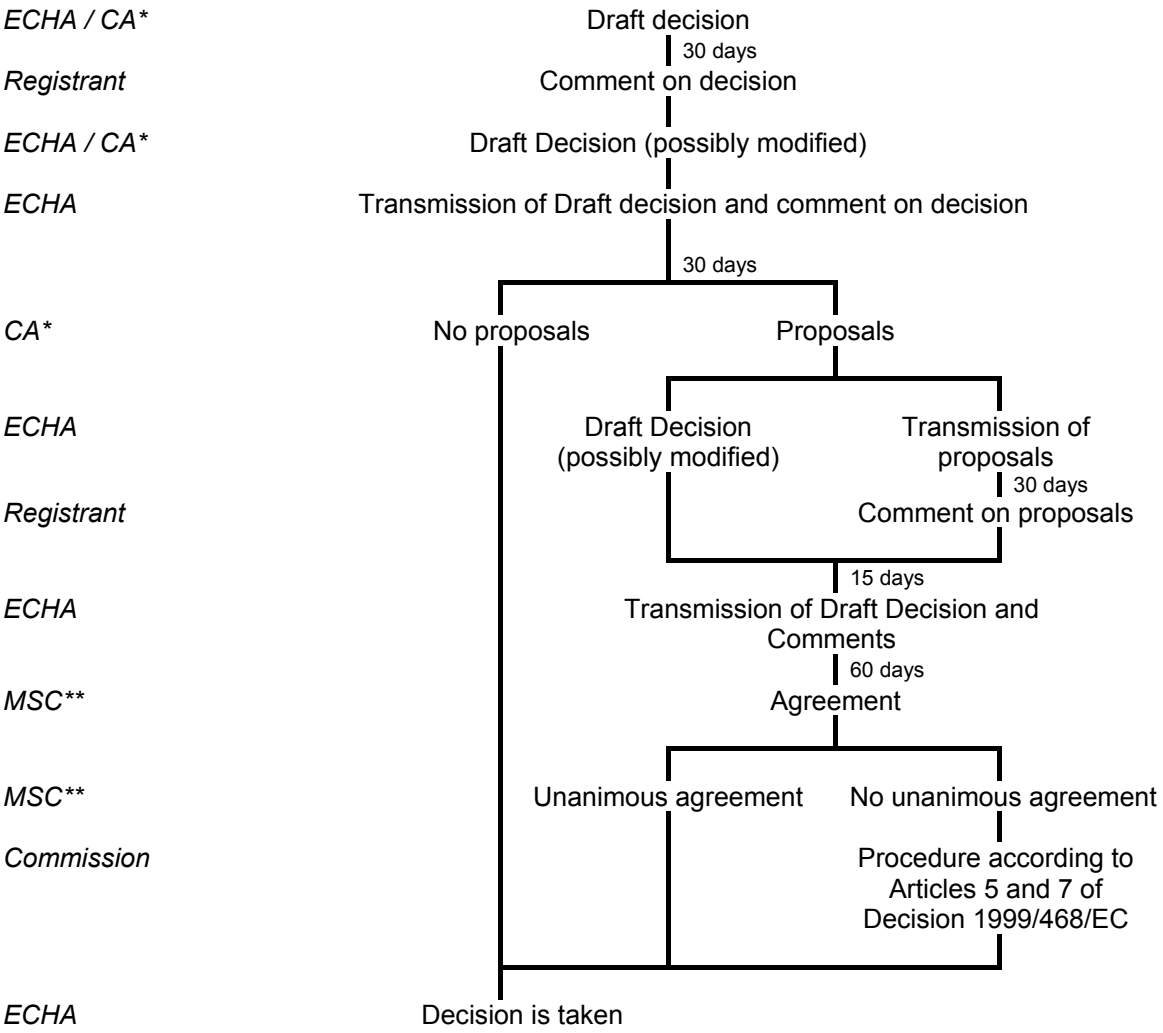
The evaluation of a substance could be based on the information obtained from the registration dossier. Structurally related substances could be included in the evaluation. The procedure is described in articles 44 till 48 of Regulation (EC) No 1907/2006. To ensure a harmonised approach the ECHA has to define criteria for the prioritization and choice of substances based on information about harmfulness, exposure and the tonnage. Additionally the ECHA has to compile a rolling action plan, in which the substances to be evaluated during the next three years are listed. It is also responsible for the coordination of the procedure whereas the evaluation is carried out by the competent authorities of the Member States. According to article 45 of the regulation the competent authority could appoint another body to act on their behalf. Furthermore the competent authority could notify to the ECHA substances, which have to be evaluated in their opinion and which are not part of the current action plan.
The substance information available is evaluated by the competent authority of the Member State. Within twelve months of the publication of the rolling action plan a draft decision has to be prepared following the procedure described in subchapter 2.3.4. If there is lack of data the draft decision is sent to the registrant to inform him about further information required for evaluation and the deadline for submission of these data. The information submitted should be evaluated by the competent authority within twelve months after receipt and a further draft decision should be made. The evaluation should be finished within twelve months of the start of evaluation or of the submission of additional data. If the deadline is exceeded, the evaluation is deemed to be finished.

2.3.4 Decision making process

During evaluation of testing proposals and dossiers any draft decision is notified by the ECHA to the registrant, who could comment on the draft within thirty days after receipt. The comments will be taken into account by the authority responsible for evaluation and the draft decision may be modified. Notwithstanding from the decision making processes above mentioned, any draft decision regarding the evaluation of the substance will be circulated together with the comments of the registrant by the concerned competent authority to the ECHA and the competent authorities of the other Member States.
The draft decision together with any comment of the registrant will be send to the competent authorities of the Member States, who may propose amendments to the decision within thirty days. If the ECHA does not receive any proposals, the draft decision will be taken.
Proposals may result in a modification of the draft decision. Moreover any proposal is sent to the registrant for comment within thirty days. Then the draft decision together with the proposed amendments will be send within fifteen days to the Member States Committee (= MSC), which is responsible for resolving potential divergences on opinions on draft decisions proposed by the Agency or the Member States. The comments of the registrant will also be taken into account by the MSC. If the

Committee reaches a unanimous agreement on the draft decision, the decision will be taken by the ECHA. In case of failure an unanimous agreement the decision will be taken by the Commission according to Articles 5 and 7 of Decision 1999/468/EC [Lit 13], having regard to the provisions of Article 8 thereof. An overview of the decision making process is presented in Fig. 3.

Fig. 3 Overview of the decision making process



* Competent authorities of the Member States
** Member States Committee

2.4 Authorisation of Substances

2.4.1 Authorisation Obligation

Annex XIV of Regulation (EC) No 1907/2006 contains a list of substances, which are only allowed to be manufactured, imported or used, if they have passed an authorisation procedure. Listed are mainly CMR-substances of category 1 and 2, PBT- and vPvB-substances. Substances with endocrine disrupting properties and PBT- and vPvB-substances, which do not fulfil the criteria mentioned in the regulation, but for which there is scientific evidence of probable serious effects to human health or the environment, could also be listed in annex XIV on a case-by-case basis.

The procedure for inclusion of substances in annex XIV is fixed in articles 58 and 59 of the REACH regulation. Priority is given to substances with PBT or vPvB properties, substances with wide dispersive use or substances of high volume. The date from which the placing on the market is prohibited unless granting of an authorisation (so called “sunset date”), the deadline for submission of the application for authorisation and review periods for certain uses are fixed during the procedure. The dossiers prepared by the ECHA or the competent authority of the Member State are published on the website of the ECHA for comments of interested parties.

If a downstream user uses a substance with authorisation obligation, he should notify the ECHA within three months of the first supply.

Article 56 of the regulation specifies reasons for placement of substances with authorisation obligation on the market without authorisation.
The substances could be exempted from the authorisation because on the basis of the existing Community legislation imposing minimum requirements relating to the protection of human health or the environment for the use of the substances, the risks are properly controlled. Here the proportionality of risk to human health and the environment related to the nature of the substance, such as where the risk is modified by the physical form has to be taken into account.
The substances can also be placed on the market without authorisation, if the “sunset date” (see above) isn’t reached. After the “sunset date” is exceeded, further placement on the market is possible only, if an application for authorisation had been submitted at the latest eighteen months before the “sunset date” and the decision on the application for authorisation isn’t taken.

These general rules do not apply for substances used in scientific research and development. For these substances annex XIV specifies the quantity exempted from the obligation. Plant protection products and biocidal products are also exempted as they have to fulfil the requirements of the concerning legislation. CMR-substances are excluded from the exemptions of article 56, too, if they are used in cosmetics and food contact materials as well as vPvB- and PBT-substances used in preparations in an amount less than 0.1 % per mass.

2.4.2 Authorisation Procedure

Responsible for taking the decisions on authorisation is the EU Commission. As mentioned in article 60 of the REACH regulation an authorisation for a substance is granted, if the risk to human health and the environment is adequately controlled. For CMR substances and for substances for which there is scientific evidence of probable serious effects to human health or the environment as mentioned in subchapter 2.4.1 and for which no threshold could be determined as well as for PBT- and vPvB-substances an authorisation will only be granted, if the socio-economic benefits outweigh the risk to human health and the environment and if there is no suitable alternative substance or technology. The same is true for PBT- und vPvB-substances, which do not fulfil the criteria of the REACH regulation.

Application for authorisation

As mentioned in articles 61 till 64 of the regulation, the application for authorisation has to be made to the ECHA by a manufacturer, importer of downstream user for one substance or a group of substances and for one or several uses. But before an application for authorisation of a substance the applicant has to proof, whether suitable alternative substances or technologies exist, which are economically and technically viable. This analysis of alternatives has to be submitted together with the request for authorisation, a substitution plan, if alternatives are available and the chemical safety report [see also subchapter 2.2.5]. A socio-economic analysis and a justification for not considering risks to human health and the environment may possibly be included, too. Reference to the documentation of an ongoing application or a authorisation granted is possible, if the subsequent applicant got the permission of the previous applicant or of the authorisation holder.

Authorisation process

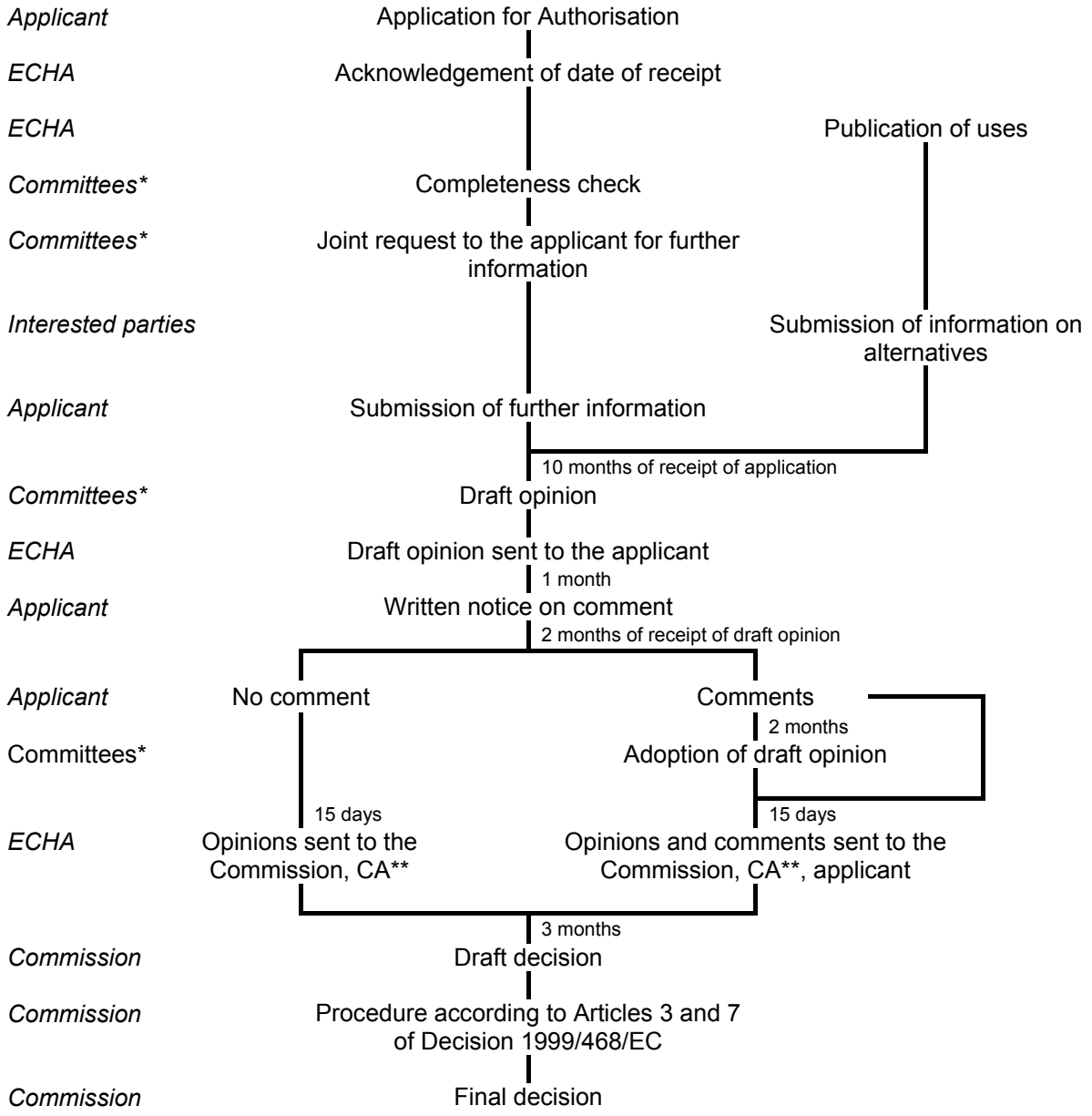
The date of receipt of the application for authorisation is acknowledged by the ECHA and the documentation is forwarded to the Committees for Risk-Assessment and Socio-economic Analysis. In a first step the completeness of the documentation is checked and a joint request to the applicant for submission of additional information is made if necessary. Information on uses of the substance is published on the website of the EMEA for submission of information on alternative substances or technologies available by interested parties.
The Committee on Risk Assessment has to evaluate the risks of the substance to human health and the environment, taking into account the risk management measures and risks arising from possible alternatives. However the Committee for Socio-economic analysis has to assess the socio-economic factors and the availability, suitability and technical feasibility of alternatives.
Within ten months the Committees for Risk-Assessment and Socio-economic Analysis have to prepare a draft opinion of the application. This draft opinion is sent to the applicant, who within one month may provide a written notice that he wishes to comment. The comments have to be sent to the ECHA within two months of receipt of the draft opinion. The opinions of the committees should be adopted within two months taking into account the comments of the applicant and within further fifteen days the opinions together with the applicant's argumentation should be forwarded to the Commission, the competent authorities of the Member States and the applicant. If the applicant does not wish to comment on the draft opinions, the opinions will be sent to the Commission and the competent authorities of the Member States within fifteen days of the end of the period within which the applicant may comment or within fifteen days of receipt of the notice of the applicant, that he does not intend to comment. Within three months a draft authorisation decision will be prepared by the Commission. The final decision will be taken by the Commission according to Articles 3 and 7 of Decision 1999/468/EC. Summaries of the Commission decision will be published. An overview of the authorisation process is presented in Fig. 4.

Review of an authorisation

An authorisation granted is valid until it is amended or withdrawn during review. Eighteen months before the expiry of the review period, which is specified in the authorisation, the authorisation holder has to submit a review report. The report contains an update of the analysis of alternatives, possibly a substitution plan, an update of the socio-economic analysis, if the risk cannot be adequately controlled, an

update of the chemical safety report, if the risk can now be adequately controlled and updates of the documentation of the original application. Notwithstanding the review period a review of the authorisation is possible at any time, if new information on alternative substances or technologies is available or if the circumstances changed and the risk to human health or the environment or the socio-economic impact are affected. In that case the authorisation holder will be given a reasonable deadline for submission of information.

Fig. 4 Overview of the authorisation process



* Committees for Risk Assessment and Socio-economic Analysis
** Competent authorities of the Member States

2.5 Guidance Documents

For facilitation of the implementation of Regulation (EC) No 1907/2006 Guidance Documents have been developed within the REACH implementation projects (= RIPs). The projects are led by the European Commission and involve Member States as well as industry and non-governmental organisations. The scope of the Guidance Documents is to support the different groups affected by the regulation in fulfilment of their obligations. The articles of the regulation related to the particular topic of the document are depicted using e.g. decision trees or examples.
In the following the Guidance Documents concerning the obligations of manufacturers, importers and downstream users are introduced briefly. The current versions of the documents are available on the homepage of the ECHA [Link 1].

Guidance on Registration [Lit 14]

The guidance describes when and how a substance has to be registered under the REACH regulation. Registration tasks and obligations are explained and useful advice is provided for preparation of the registration dossier. A short introduction is given into IUCLID 5 with reference to the guidance concerned.

Guidance on IUCLID [Lit 15]

The guidance is a detailed user manual for the software, which is mandatory for submission of dossiers. It describes how to use IUCLID 5 and how to prepare the dossier for different REACH requirements.

Guidance on Pre-Registration

This document is not yet available. On the homepage of the ECHA it will be referred to the Guidance on Data sharing, which contains a chapter on pre-registration.

Guidance on Data sharing [Lit 16]

In the guidance the mechanisms of data sharing for phase-in and non-phase-in substances are described. In addition to the above mentioned chapter on pre-registration, the categorization of a substance as “same” to another substances is discussed referring to the Guidance for identification and naming of substances under REACH. The details on the SIEF, the Inter-SIES rules (with reference to the Guidance on information requirements under REACH), the joint submission of data, proposals for the cost sharing and the rules to be regarded during information sharing in terms of competition law are also carried out in the guidance. Furthermore the difference between a SIEF and a consortium, which is also a possible form of cooperation between SIEF members, is represented and the term “Confidential Business Information” is defined.

Guidance for intermediates [Lit 17]

The different categories of intermediates are defined and the “strictly controlled conditions”, mentioned in the regulation are pointed out with examples. Additionally, the guidance document contains a list of issues, which should be taken into account when checking that the manufacture is done under strictly controlled conditions.

Guidance for monomers and polymers [Lit 18]

In the Guidance Document detailed definitions for monomer, polymer and manufacture of polymers are given. The tasks and obligations regarding manufacture/import are carried out, whereas emphasis is given to registration, possible restrictions, classification and labelling and information in the supply chain. A short section deals with analytical methods, which are suitable for identification of polymers and determination of monomers or other reactant in polymers.

Guidance on SR&D and PPORD [Lit 19]

Among the definitions of “scientific research and development” and “product and process oriented research and development” the tasks and obligations especially concerning to substances for PPORD manufactured and imported in quantities less and more than 1 ton per year are mentioned. Furthermore the notification of PPORD substances and the update of a notification dossier using IUCLID 5 are carried out.

Guidance on classification and labelling notification

This guidance document is not yet available.

Guidance on requirements for substances in articles [Lit 20]

This guidance document summarises the paragraphs of the REACH regulation concerning articles. It helps to decide whether a product has to be classified as article or not. Attention is paid to borderline regarding the change from being a substance/preparation to being an article as well as to borderline between substances/preparations in special containers or special carrier materials and substances/preparations being part of articles. Moreover the guidance assists suppliers in deciding if and how they have to fulfil the different notification, registration or communication requirements.

Guidance for Downstream Users [Lit 21]

This guidance describes very detailed the obligations of downstream users. Using flowcharts the workflow concerning communication upstream and downstream is outlined. The fixation of the downstream user’s use in the Material Safety Data Sheet (= MSDS) and the consequences, if the use is not covered, are also pointed out. Emphasis is also given to the check of compliance with the exposure scenario, the making of a chemical safety report and the collection of information on uses.

Guidance on the preparation of an application for authorisation

This guidance is not yet available. It will be developed within RIP 3.7.

Guidance for identification and naming of substances under REACH [Lit 22]

The guidance supports the recording of the identity of substances within the context of the REACH regulation using e.g. EINECS, structural formula or the composition. It provides also guidance on how to name a substance. As mentioned above criteria for checking the “sameness” of substances are listed in the document. Additionally sources of further information (databases, websites, handbooks) that can be useful for finding the appropriate information required for substance identification are referred to.

Guidance on how to comply with the provisions of the new regulation on classification, packaging and labelling of substances and mixtures

This guidance is not yet available. It will be developed within RIP 3.6.

Guidance for the preparation of the chemical safety report

This guidance is not yet available. It will be developed within RIP 3.2.

Guidance on information requirements under REACH [Lit 23]

The guidance document describes the information requirements under REACH with regard to substance properties, exposure, use and risk management measures, and the chemical safety assessment. It consists of “sub-guidances”, which are divided into “concise guidance” (part A to G) and “supporting reference guidance” (R.2 to R.20). Assistance is given to the collection of the available information regarding the intrinsic properties of the substance to be registered, to the assessment of this information against the requirements specified by REACH, to the identification of data gaps and to the generation of the additional information required to fill the data gaps. The guidance also aims in conducting Chemical Safety Assessments and preparing Chemical Safety Reports. The purpose of the “concise guidance” is to support the processes needed to meet the information requirements on intrinsic properties of substances to be registered, and where relevant to carry out a chemicals safety assessment. The purpose of the “reference guidance” is to provide in-depth scientific and technical advice. Both types of guidances are closely related.

Guidance on socio economic analysis - restrictions [Lit 24]

Through this document technical guidance is given to anyone, who is intended to undertake a socio-economic analysis to support a restriction proposal or to react to the publication of a restriction proposal. Using examples, checklists and figures the different steps of the socio-economic analyses are described very detailed. Additionally the necessary tools e.g. valuation techniques, assessment tools are summarised.

Guidance on priority setting for evaluation

This guidance is not yet available. It will be developed within RIP 4.5.

3. Is the pharmaceutical industry affected? – Some examples

According to article 2 paragraph 5 of Regulation (EC) No 1907/2006 substances used in medicinal products following regulation (EC) No 726/2004 [Lit 26], Directive 2001/82/EC [Lit 27] and Directive 2001/83/EC [Lit 28] as amended are exempted from the registration obligation under REACH. Therefore at first sight the pharmaceutical industry seems not to be affected by the legislation, but the situation is more complex than intended; this will be shown in a few examples.

Example 1

As mentioned above, substances, which are present in a medicinal product, are exempted from the REACH regulation. However, any substance that is used during the manufacture and that is not a component of the medicinal product (e.g. machine oil) has to fulfil the requirements of the regulation. Substances that are used during manufacture and that are not contained in the finished product as e.g. solvents for granulation or coating, also have to comply with the regulation [Lit 25].

If the substances are imported from Non-EU countries and the manufacturer hasn't a representative within the EU, he isn't able to (pre-) registrate the substance and therefore the substance won't be available after expiration of the concerned deadline. Further import and use is only possible, if the marketing authorisation holder (or another person with full responsibilities) acts as importer and fulfils the REACH obligations. Alternatively the marketing authorisation holder (= MAH) could use the substance from another supplier established within the EU, who will (pre-) registrate the substance. If the MAH wants to (pre-) registrate himself, he should take into account the emerging costs as well as the human resources needed.

Another problem appears, if the quantity of substances imported to the EU is marginal in comparison to the amounts marketed outside the EU. The manufacturer could possibly be no longer interested in further marketing in the EU and he wouldn't therefore (pre-) registrate the substances for reasons of economy or human resources. Then, after expiration of the timeline for (pre-) registration, the substances won't be available. Now the marketing authorisation holder has the options mentioned in the previous paragraph.

Example 2

If an excipient, which is used in medicinal products, is also used for other purposes e.g. in cosmetics, in the automobile sector or the colouring industry, this substance is still falling under the scope of the regulation. Though for calculation of the tonnage band the amount used in medicinal products will be disregarded, the manufacturer has to provide human and economic resources for fulfilment of the obligations of the REACH regulation [Lit 14]. If he is not willing to do so and if, in addition, the marketing of the substance for use in medicinal products only is not remunerative, the substance won't be produced any longer and therefore won't be available.

The MAH now has the possibility to change the supplier or to replace the excipient in the medicinal product with another. The latter will be associated with a change of the marketing authorisation. If an excipient should be replaced, research on galenics has to be done. Furthermore referring to Commission Regulation (EC) No 1084/2003 [Lit 29] and Commission Regulation (EC) No 1085/2003 [Lit 30] the dissolution has to

be tested on at least two pilot batches. Stability studies have to be performed on at least two pilot or production batches and at least three months stability data including the commitment of finishing the studies have to be provided. If the conditions (comparable dissolution profiles, adequate stability data) are not fulfilled the excipients can't be regarded as comparable so that the change in the excipients won't be classified as type IB but as type II variation. For the latter further research has to be done.

Example 3

In contrast to medicinal products, medical devices according to Council Directive 93/42/EEC [Lit 31] are not exempted from Regulation (EC) No 1907/2006. Active ingredients as well as excipients contained in the finished medicinal products are supposed to be proven regarding their risk on human health and the environment during the authorisation procedure, whereas substances in medical devices are subject to the evaluation under REACH. Through this procedure, substances in class III medical devices are checked twice regarding their risks, because these have been reviewed during conformity assessment procedure [Lit 32, Lit 33]. However substances in class I medical devices are not evaluated by an independent institution until the REACH regulation coming into force. For these substances the review on the risks makes sense.

4. How to deal with the REACH regulation? – An approach

As it has been shown in chapter 3, the pharmaceutical industry has to deal with Regulation (EC) No 1907/2006 and has to implement suitable actions to guarantee the availability of substances for pharmaceutical usage.

Exemplary for the different constellations within the pharmaceutical industry (company size, production and synthesis facilities) an approach to deal with the obligations of the REACH regulation will be described using the example of a medium-sized enterprise without own production facilities.

The different steps to be done will be presented in subchapter 4.1. The following subchapters 4.2 and 4.3 will illustrate some specifics for flavourings and primary packaging material.

4.1 Steps to be done in the context of REACH

To guarantee the availability of the substances used in medicinal products and during the manufacture, different steps during the “pre-pre-registration”, the pre-registration and the registration phase have been taken into account. The main steps are mentioned in Fig. 5 and Fig. 6. They should be coordinated by an appointed person responsible for REACH.
It has to be pointed out, that the obligations of the REACH regulation only apply to substances manufactured or imported in quantities of one ton or more per year. But in the present case the annual amount of substance is unknown and the availability of all substances should be guaranteed. Therefore, it seems to treat all substances the same manner.

4.1.1 Steps needed during “pre-pre-registration” and pre-registration phase

Inventory of substances

The first step in dealing with the REACH regulation is the compiling of an inventory, in which the substances contained in the finished medicinal product as well as substances used during manufacture are listed. It is the most important instrument for monitoring of the following steps. Special attention has been paid to substances, which will be chemically modified before use for manufacture. For these substances a registration under REACH is mandatory, whereas the chemically modified substance, which can be found unchanged in the finished product, is exempted from the registration obligation.

At least the following information should be enclosed:

- Name of the substance (including INN and trade name)
- Name of the medicinal product
- CAS number
- EINECS number
- Listing in annex IV and V of the regulation
- Contact details of the contract manufacturer
- Contact details of the supplier
- MSDS.

Among the *substance name* currently used e.g. in the dossier or in the batch record, the INN (= International Nonproprietary Name) as well as the trade name should be part of the list. That way the responses from contract manufacturers or suppliers, who often use different names, could be better assigned. Because one excipient may be used in different medicinal products the *name of the medicinal product* should also be mentioned in the inventory to avoid confusion. For search of substances at the website of the ECHA the *CAS* and the *EINECS number* will be helpful. They can be found on the website of the ECB (= European Chemicals Bureau) in the database ESIS (= European chemical Substances Information System) [Link 2]. In another column the substances *listed in annex IV and V* of the REACH regulation should be tagged. Annex IV and V contain substances, which are exempted from the obligation of registration, because the information available is sufficient and the substances are considered to cause minimal risk (e.g. glucose, sucrose). For the moment substances of the inventory, which are listed in annex IV and V, could be regarded as carried out. But changes of the annexes, which are possible easily, have to be controlled closely and, if substances of the inventory are deleted from the annexes, the substances have to return into the monitoring. Information on the *MSDS* should also be part of the inventory. After completion of the registration procedure the "identified uses" of the substance have to be mentioned in the MSDS. Therefore the marketing authorisation holder has to ensure, that his use will be included in the MSDS. Otherwise he has to register his own use including e.g. the preparation of a chemical safety report. A template for a substance inventory can be found in Annex 4 of this thesis.

Request to the contract manufacturer

After getting an overview of the substances in the second step a request should be sent to the contract manufacturers. Here it has to be pointed out, that the contract manufacturer isn't a manufacturer in terms of the regulation. Manufacturer according to the REACH regulation means a person, who manufactures a substance within the EU. The contract manufacturer, who produces a preparation using different substances, therefore, could be generally classified as downstream user. Only if he imports a substance from a non-EU country, he will be considered as importer [Lit 25].

With the request the contract manufacturer should be asked about the following:

- Activities regarding the REACH regulation already done
- Planned activities regarding REACH
- Contact details of the suppliers for the substances contained in the finished product
- Name of the substances used during manufacture and contact details of the suppliers.

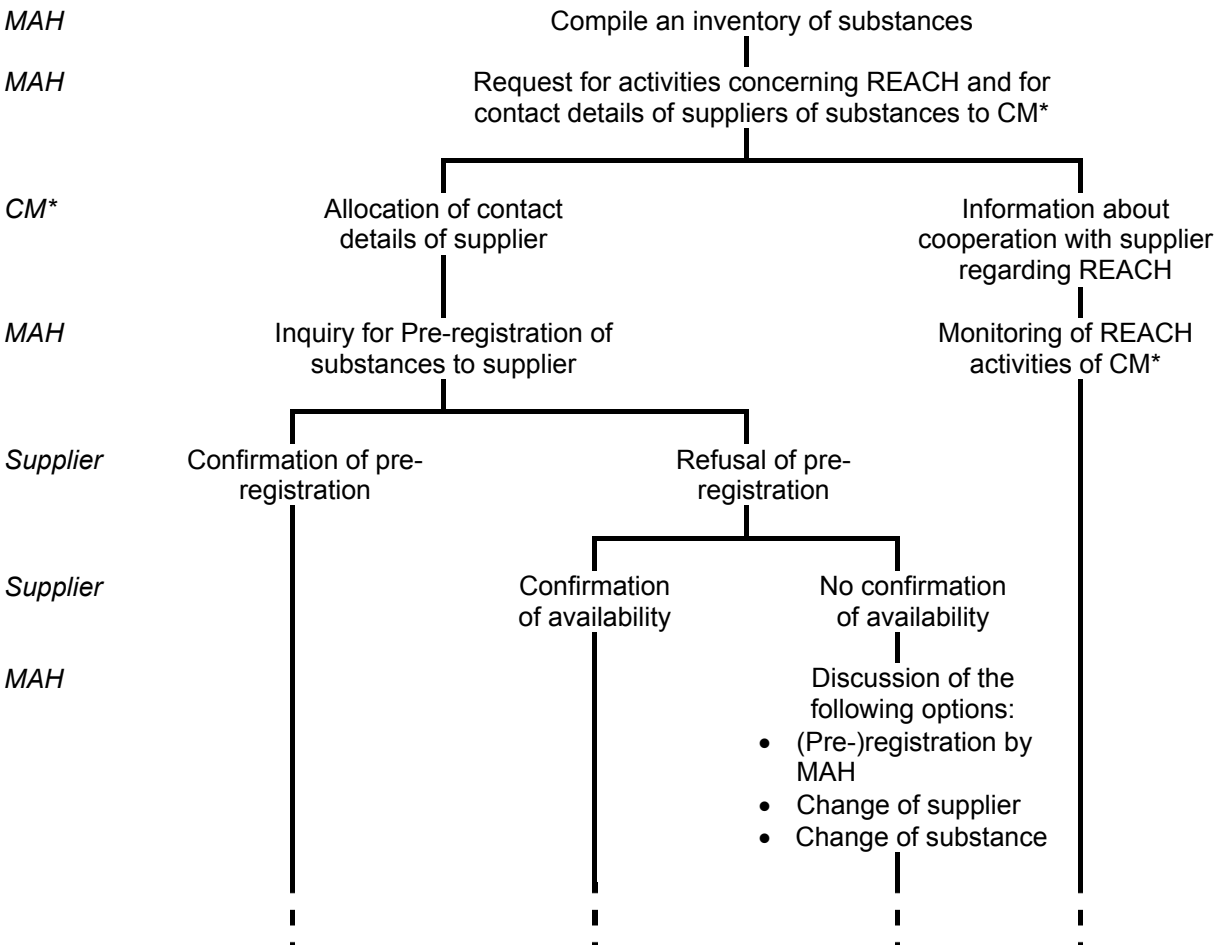
Contract manufacturers of medicinal products frequently assume that they are not affected by the REACH regulation because of the exemption of medicinal products. Therefore, at first, a familiarity of the contract manufacturer for the subject is necessary. A few introductive sentences in the letter would be helpful. However, because of narrow economic and human resources the contract manufacturer usually wouldn't be willing to deal with REACH.

Anyhow, if the contract manufacturer tells the MAH, that he is in close cooperation with his suppliers regarding REACH, the MAH should monitor these activities especially

regarding statements on the availability of the substances. Although the supplier won't ensure the availability of the substance before the expiration of pre-registration phase and the formation of the SIEFs, it is advisable to keep in touch with the contract manufacturer.

In the case that the contract manufacturer transmits the contact details of the different suppliers to the MAH, the latter could contact the suppliers on his own, as mentioned in the next paragraph.

Fig. 5 Overview of the steps to be done during "pre-pre-registration" and pre-registration phase



* Contract manufacturer

Request to the supplier

The MAH will send a request to the supplier for clearing up the following items:

- Intention to (pre-) registrate the concerned substance
- Availability of the substance after expiration of the (pre-) registration phase.

Because the supplier does not maintain business contacts with the MAH a short introduction is necessary containing e.g. the name of the substance and of the contract manufacturer, who purchases the substance. In return for the information given by the supplier, the latter should be told of the usage of the substance and – whenever possible- of the annual need. Hereby he will get an overview of the different applications of his substance and he is able to calculate the tonnage band, if

he has to pre-registrate the substance, and therewith the registration date and the documentation to be submitted. To underline the cooperation between MAH, supplier and contract manufacturer, the information obtained from the supplier should be circulated to the contract manufacturer.
A helpful instrument for the exchange of the above mentioned information is a questionnaire, which summarizes the current situation concisely and enables a prompt reply. A template for a questionnaire can be found in Annex 5 of this thesis.

If the supplier confirms, that he would pre-registrate the substance, the MAH can wait for the expiration of pre-registration phase, because the pre-registration can be regarded as confirmation for the further availability of the substance. If the availability of the substance is confirmed by the supplier without pre-registration e.g. if the substance is only used for pharmaceutical purposes the MAH also has to do nothing for now.

Otherwise, if the supplier refuses to pre-registrate the substance and additionally if he does not affirm the further availability of the substance, the MAH should discuss the following options in-house:

- Pre-registration of the substance by MAH
- Change to a supplier, who pre-registrated the substance
- Change of the substance.

The MAH could decide to pre-registrate the substance on his own. Then he has to submit the data necessary to the ECHA during the pre-registration phase (01.06.2008 – 01.12.2008). Because of the parallels to a “post-pre-registration” or registration, further details of this option will be discussed in subchapter 4.1.2. A possible change of the supplier or of the substance will also be discussed in the next paragraph.

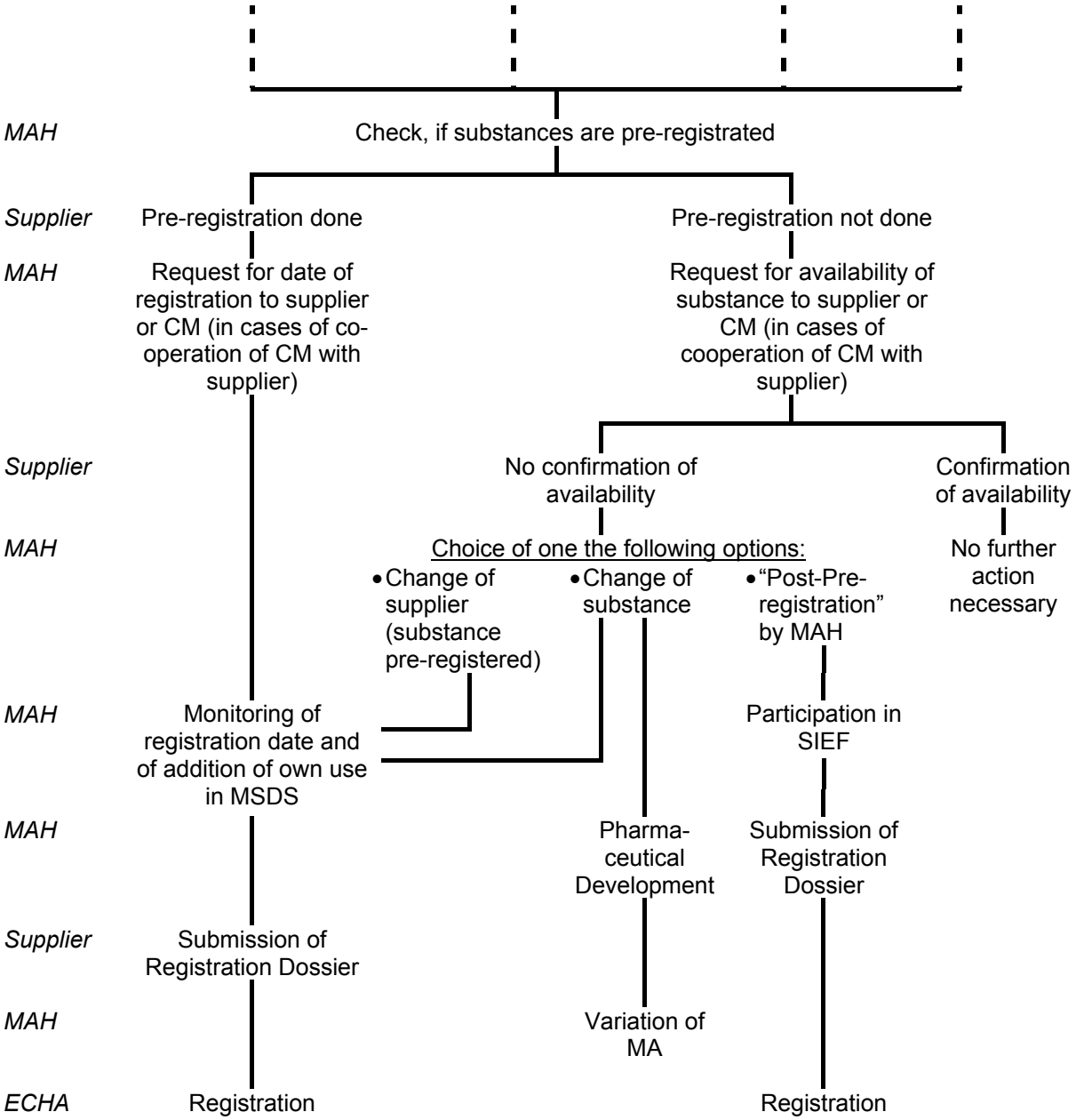
4.1.2 Steps needed during registration phase

Check for pre-registration

From January 1st 2009 that is after expiration of the pre-registration phase the substances, which are pre-registrated, are published on the website of the ECHA together with the proposed registration date. As mentioned above, the manufacturers or importers, who did the submission for pre-registration, stay incognito. Substances, which are obliged to be pre-registrated and for which no submission was done, are not allowed to be marketed any longer.

Now the MAH should check, if the substances used in the medicinal products are pre-registrated. Via CAS- and EINECS-number this will easily be possible. Even if the supplier hadn’t pre-registered the substance, but confirmed the availability of the substance, the MAH could inform himself, if there are alternative manufacturers and/or importers, who pre-registrated. However, if no one pre-registrated the substance concerned, according to article 28 paragraph 5 of the regulation the MAH may notify the ECHA of his interest in the substance, his contact details and the details of his current supplier. If a potential registrant is interested in the substance, the contact details of the MAH will be provided to him.

Fig. 6 Overview of the steps to be done during registration phase



Second request to the supplier or the contract manufacturer

If the check of pre-registration is completed the MAH should send a second request to the supplier or to the contract manufacturer (in cases of cooperation between supplier and contract manufacturer). Depending on the status of the substance, the contract manufacturer will ask for the following issues:

- Substance is pre-registrated:
  - Estimated date of submission of registration dossier
  - Estimated usage for substance
- Substance is not pre-registrated:
  - Further availability of the substance

If a pre-registration is carried out, the supplier has signalled therewith, that he is interested in the further marketing of the substance and that he will also submit a

registration dossier for the substance. But it is advisable for the MAH to monitor, if the registration really occurred (within the estimated time phase). When the supplier signals, that the marketing of the substance will be ceased, the MAH could “post-pre-registrate” the substance on his own at the latest twelve months before expiration of the proposed registration date. Further details on this subject can be found below.

The second issue asked is at least as important as the request for the registration date. The usage of a substance is only allowed, if this use is registrated as “identified use”. According to article 37 of Regulation (EC) No 1907/2006 each downstream user should inform the manufacturer or importer about his usage of the substance. The latter will then include the use in the registration documentation, if sufficient information is provided and if he isn’t unable to include it as an identified use for reasons of protection of human health or the environment. Otherwise the MAH (and the ECHA) will be informed about the objections. Than the MAH possibly has to prepare a chemical safety report regarding his own usage, carry out a risk assessment and inform the ECHA on his part.

The further availability of the substance should be asked for, if it is not pre-registrated. As mentioned above the substance could be exempted from (pre-) registration, if it is only used for e.g. medicinal products. In this case the supplier will confirm the availability, so that further activities of the MAH are not necessary.

If no confirmation is given by the supplier, the MAH has to decide, which of the options discussed during the “pre-pre-registration“ and pre-registration phase will fit best.

Option 1: Switch of supplier
One possibility is to switch to a supplier, who pre-registered his substance, whereas the fact, that the name of the supplier isn’t published on the website of the ECHA, hinders the search. If a new supplier is found and he has signalled interest in further marketing via pre-registration, this is no guarantee for availability of the substance. Therefore the MAH has to monitor the regulatory activities of the new supplier closely and if necessary has to “post-pre-registrate” the substance on his own.

Option 2: Switch of substance
In the case, that the substance isn’t available any longer, because it isn’t pre-registered and additionally it isn’t marketed for exempted purposes or if the ceasing of the marketing is foreseeable and the MAH doesn’t want to registrate the substance on his own, he will change the excipient. Here he could prefer a pre-registered substance for above mentioned reason.
The switch is associated with complex development work. E.g. research on galenics has to be done. The compatibility of the substance with the other components of the medicinal product has to be tested as well as the dissolution profile. Where necessary a bioequivalence or bioavailability study has to be performed. Additionally the manufacture and the analysis of the product probably need to be adjusted (including validation), a possible change in the impurity profile has to be determined and the stability of the product has to be proven. If the results are sufficient, the marketing authorisation will be amended.

Option 3: Registration of the substance

The third option is a registration of the substance by the MAH. If the substance is imported for pharmaceutical purposes only and if it will be contained unchanged in the finished medicinal product, a registration is not necessary. But if the MAH needs the substance e.g. for use in a medical device or if it will be modified during manufacture, the registration of this substance is mandatory. It has also to be pointed out, that a registration can only be performed by manufacturers or importers [Lit 34]. An enterprise without own production facility therefore could only act as importer of the substance from Non-EU countries. If the MAH has the intention to import the substance, there are the following possibilities to submit the data to the ECHA. The MAH could pre-registrate the substance during pre-registration phase (01.06.2008 till 01.12.2008). According to article 28 paragraph 6 he could also "post-pre-registrate" the substance after 01.12.2008, if he imports it for the first time. He has to submit the information within six months of the first importing and not later than twelve months before the expiration date of the related tonnage band to benefit from the transition periods laid down in the regulation. If the MAH isn't interested in using the transition period, he could directly apply for a registration of the substance.

In the case, that the MAH wants to use the transition period, he will submit the data mentioned in article 28 of the REACH regulation to the ECHA on time and through this becomes participant of a SIEF. According to the regulation the registrants for the same substance have to cooperate, but a definition for the "sameness" of substances isn't given. The Guidance for identification and naming of substances under REACH [Lit 22] will provide an indication for correlation of substances. However several questions remain open and may provoke discussions [Lit 25]. If the MAH is successfully assigned to the concerned SIEF and before he will discuss the exchange of studies or the need for further studies, he has to conduct contract negotiations regarding the rules within the SIEF. The data and cost sharing has to be settled as well as the sharing of information regarding EC competition law. The third point taken into consideration is the protection of the own confidential business information. Here it is recommended to appoint a third party representative without responsibilities with respect to the regulation obligations for masking the company's identity [Lit 34]. After conclusion of the contract, the discussion on the scientific data starts. The members of the SIEF should reach a consensus e.g. on the studies to be performed, on the data to be submitted and on the "lead registrant", who will submit a part of the data in the name of the other participants of the SIEF. When the technical dossier and the chemical safety report are completed, the submission of the data will take place partly by the lead registrant and partly by all registrants as mentioned in article 11 of the regulation within the given timeframe using the software IUCLID 5. It has to be taken into account, that the use of this complex software is difficult and requires a training course as well as the appropriate technical infrastructure. After the submission is finished, the completeness of the documentation will be checked by the ECHA and a registration number will be assigned after successful termination. Furthermore the MAH has to update the dossier as fixed in article 22 of the REACH regulation.

Although the MAH will only registrate his intended use, the costs and the work load could become very high. As participant of the SIEF the MAH has to share the costs of all the data required for the proposed tonnage band. As importer he won't have own data, so that he possibly has to pay for all studies needed for registration. Additionally the cooperation in the SIEF, the preparation and submission of the registration dossier (including the training on IUCLID 5) will be personnel-intensive. Especially if only very few substances will be registrated by the MAH and the

experience in preparation of dossiers will stay marginal, it is advisable to place an order with a consultant or a CRO (= contract research organisation).

4.2 Flavourings – To be considered

Flavourings, which are contained in a medicinal product, are as exempted from the REACH regulation as other ingredients. Additionally according to article 2 paragraph 5 (b) of the Regulation (EC) No 1907/2006 flavourings used in foodstuff within the scope of Council Directive 88/388/EEC [Lit 35] and Commission Decision 1999/217/EC [Lit 36] are not affected by REACH. However flavourings, which are used for other purposes or which are used in foodstuff, but do not comply with the before mentioned legislation, have to fulfil the obligations of the regulation. At first this does not seem to affect the MAH of a medicinal product, but the major part of flavourings is used for foodstuff. If these do not comply with the food legislation and the fulfilment of the REACH obligations is too cost-intensive and if the further marketing for pharmaceutical purposes only isn't profitable, these flavourings won't be available any longer. Than a change of the flavouring, which will cause development work as mentioned in subchapter 4.1.2, is inescapable. Special attention has to be paid to the compatibility of the flavouring with the other excipients and to the stability of the flavouring as well as of the medicinal product. Additionally, flavourings, which do not comply with the legislation, often contain ingredients, which are classified as critical by the EU, so that the ceasing from the market is foreseeable. Therefore besides the guarantee of availability it is important for the MAH to know, if the flavourings used in the medicinal product are in accordance with Council Directive 88/388/EEC and Commission Decision 1999/217/EC and he should ask this in addition to the above mentioned questions.

4.3 Primary Packaging Material – To be considered

The PPM (= primary packaging material), especially the plastics, also have to be outlined in a separate chapter. As mentioned in article 2 paragraph 5 (a) of Regulation (EC) No 1907/2006 substances used in medicinal products are exempted from the obligations. Up to know it is debatable, if this also applies to the primary packaging material used for medicinal products. The exemption for medicinal products is based on the fact, that the risks for humans and the environment are evaluated sufficiently during the authorisation process [Lit 32]. However, it is in question, if the documentation of the PPM in module 3.2.P.7 of the medicinal product's dossier is detailed enough for an adequate evaluation. Just for plastics, which contain a lot of different substances, normally the information in the dossier isn't as detailed as required. As long as PPM are not definitely exempted from REACH, it has to be assumed that the substances contained fall within the scope of the regulation. If some of the substances in PPM are not available any longer, because the manufacturer or importer of the substance don't want to deal with REACH, the manufacturer of the PPM has to change the composition of his product. The latter could influence the finished medicinal product for reasons of e.g. migration from substances of PPM into the medicinal product and adsorption of components of the medicinal product at the PPM. If the composition changed, the MAH has to perform extraction and interaction studies and new stability studies under ICH conditions with the finished medicinal product.
Therefore the MAH should send a request to the supplier of the PPM and ask not only for pre-registration and availability but also for changes in the composition to be informed on the change of PPM in good time.

5. Conclusion and outlook

In the previous chapters is has been shown, that the pharmaceutical industry is affected by Regulation (EC) No 1907/2006, although substances used in medicinal products are exempted from the regulation. From the widespread spectrum within the pharmaceutical industry the medium-sized enterprise without any own production facilities has been selected to provide strategies how to deal with these isues.

As with other regulations, the REACH regulation needs some interpretation to solve problems. This should take place within the REACH Implementation Projects, where Guidance Documents are developed. As mentioned in subchapter 2.5 of this thesis many Guidance Documents are not available until now, whereas the lack of the Guidance on Pre-registration is the most severe at the moment. It is assumed, that in the near future the documents will be published. Therefore each company affected by REACH should monitor closely the publication of guidances on the website of the ECHA [Link 1].

The REACH regulation came into force on June 1st 2007, the pre-registration phase started recently. Experience with the pre-registration and registration procedure as proposed in the regulation including e.g. the submission of data via IUCLID 5 and the cooperation in the SIEF nearly does not exist until now. Possibly the proceedings and the regulation will be modified based on the experiences gained.

For each company it is important to find out, if and how they are affected by REACH. Therefore they are advised to compile an inventory of all substances used for their products, to decide whether they are manufacturer, importer or downstream user regarding each individual substance and to define a process to guarantee the availability of the substances as soon as possible. For this objective, a close cooperation between the different partners dealing with a substance is essential. The proceedings of the companies will differ depending on the company size, the production or synthesis facilities, the economic and human resources and especially the willingness to deal with REACH. But it has to be pointed out, that the consequences of an inadequate handling with the topic could be severe.

6. Summary

At June 1st 2007 Regulation (EC) No 1907/2006 came into force. The regulation is also called REACH regulation, whereas REACH means **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals. It stands for a complete revision of the European chemicals legislation. Many directives and regulations concerning chemical substances and preparations are modified or overruled. Until then there were two classes of chemicals: 97 % of substances for which nearly no data on risk for human health and the environment was provided and 3 % of substances, which were evaluated regarding their risks. Now with the REACH regulation the requirements for all chemicals are harmonized, whereas transition periods till 2018 are provided.

The regulation describes a registration procedure for chemical substances, substances used in preparations or substances, which are part of an article. The registrant has to submit a dossier at the ECHA (= European Chemicals Agency), whose extent depends on the hazardousness of the substance and the annual quantity manufactured or imported. If he wants to take the transition period he additionally has to pre-registrate the substance and work together with other registrants of the same substance in a SIEF (= Substance Information Exchange Forum). The registration dossier is checked for completeness by the ECHA and a certain percentage of substances is also evaluated, mainly based on the documentation submitted. Dangerous substances have to be authorised by the ECHA before further marketing.

At first sight the pharmaceutical industry seems not to be affected by REACH, because substances used in human or veterinary medicinal products are exempted from the regulation. But there are several reasons for dealing with the subject, e.g.

- Substances contained in the finished medicinal product are exempted from the regulation, whereas substances used during manufacture e.g. solvents for granulation or machine oil are concerned.
- If substances are mainly used for other purposes e.g. in the automobile sector or the colouring industry, this quantity is still falling under the scope of the regulation. In the case that the manufacturer/importer doesn’t want to deal with REACH and he also won’t market the substance for pharmaceutical purposes only, the substance won’t be available any longer.
- Medical devices, which are often also part of a portfolio of a pharmaceutical company, have to fulfil the obligations of the regulation without exemption.

For a medium-sized enterprise without any own production facilities an approach for dealing with the REACH regulation and guarantee the further availability of substances is made. The activities recommended take place during the “pre-pre-registration” and the pre-registration as well as during the registration phase. Emphasis is given on a close cooperation between the supplier, the contract manufacturer and the marketing authorisation holder.

7. References and Useful Links

References

Lit 1 Treaty of the European Union, Official Journal of the European Union, C 321 E/1-331, 29.12.2006

Lit 2 Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations, last amended on February 25th 2004

Lit 3 Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC, last amended on August 7th 2001

Lit 4 Sunder-Plassmann N. Die neue EG-Verordnung zum Chemikalienrecht REACH und ihre Relevanz für die Pharmaindustrie, PharmInd 69 (8), 937-40 (2007)

Lit 5 Brochure „REACH-Info 1, Erste Schritte unter der neuen EU-Verordnung REACH“, Editor: BAUA (Juli 2007)

Lit 6 Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

Lit 7 Council Directive 92/32/EEC of 30 April 1992 amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

Lit 8 Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances

Lit 9 Brochure „REACH-Info 4, Neustoffe und REACH“, Editor: BAUA (March 2008)

Lit 10 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

Lit 11 Brochure „REACH-Info 2, Besonderheiten bei Zwischenprodukten und Stoffen in Forschung und Entwicklung“, Editor: BAUA (September 2007)

Lit 12 Brochure „REACH-Info 3, Besonderheiten bei Polymeren und Monomeren“, Editor: BAUA (December 2007)

Lit 13 Council Decision of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission (1999/468/EC)

Lit 14 ECHA Guidance Document: Guidance on registration (April 2008)

Lit 15 ECHA Guidance Document: Guidance on IUCLID (June 2007)

Lit 16 ECHA Guidance Document: Guidance on data sharing (September 2007)

Lit 17 ECHA Guidance Document: Guidance for intermediates (February 2008)

Lit 18 ECHA Guidance Document: Guidance for monomers and polymers (March 2008)

Lit 19 ECHA Guidance Document: Guidance on Scientific Research and Development (SR&D) and Product and Process Oriented Research and Development (PPORD) (February 2008)

Lit 20 ECHA Guidance Document: Guidance on requirements for substances in articles (May 2008)

Lit 21 ECHA Guidance Document: Guidance for downstream users (January 2008)

Lit 22 ECHA Guidance Document: Guidance for identification and naming of substances under REACH (June 2007)

Lit 23 ECHA Guidance Document: Guidance on Information Requirements and Chemical Safety Assessment (May 2008)

Lit 24 ECHA Guidance Document: Guidance on Socio-Economic Analysis - Restrictions (May 2008)

Lit 25 Brixius K, Maur A. REACH: Schnittstellen und Handlungsbedarf für die pharmazeutische Industrie. Ein Leitfaden für die Praxis. PharmR 7, 277-84 (2007)

Lit 26 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Lit 27 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, last amended on April 30th 2004

Lit 28 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, last amended on April 30th 2004

Lit 29 Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State

Lit 30 Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93

Lit 31 Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amended on September 21st 2007

Lit 32 Wimmer M. Neues Europäisches Chemikalienrecht (REACH), Eine Herausforderung auch für die Medizinprodukteindustrie, Teil 1, MPJ 14 (2), 64-9 (2007)

Lit 33 Wimmer M. Neues Europäisches Chemikalienrecht (REACH), Eine Herausforderung auch für die Medizinprodukteindustrie, Teil 2, MPJ 14 (3), 119-24 (2007)

Lit 34 Fink D, Hanschmidt A, Lulei M. REACH: Die Bedeutung der Vorregistrierung, StoffR 4, 152-8 (2007)

Lit 35 Council Directive 88/388/EEC of 22 June 1988 on the approximation of the laws of the Member States relating to flavourings for use in foodstuffs and to source materials for their production,
last amended on February 15th 1991

Lit 36 Commission Decision 1999/217/EC of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council

Useful Links

Annotation:
In this chapter additional links can be found, which are not mentioned in chapters 1 till 6, but which may be helpful for general information, research of substances or specific problems.

Link 1 Homepage of ECHA: http://echa.europa.eu/home_en.html

Link 2 Homepage of ECB: http://ecb.jrc.it/esis

General Information

Homepage of BAUA: http://www.baua.de

Homepage of BfR (Bundesinstitut für Risikobewertung):
http://www.bfr.bund.de

REACH Information Portal of UBA (Umweltbundesamt):
http://www.reach-info.de

Information on Substances

Database ChemID Plus Advanced (United States National Library of Medicines): http://chem.sis.nlm.nih.gov/chemidplus/

Answers to specific questions

REACH Helpdesk of BAUA: http://www.reach-helpdesk.de
(General problems)

REACH Helpdesk of Institut ASER e.V.: http://www.reach-net.com
(General problems, Links to further German and European helpdesks)

Working Group REACH of BAH: reach@bah-bonn.de
(Pharmaceutical problems)

8. Annexes

*Annex 1 Overview of the physicochemical information required for registration depending on the quantity of substance manufactured or imported annually**

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Physicochemical information				
State of the substance at 20°C	X	X	X	X
Melting/freezing point	X	X	X	X
Boiling point	X	X	X	X
Relative density	X	X	X	X
Vapour pressure	X	X	X	X
Surface tension	X	X	X	X
Water solubility	X	X	X	X
Partition coefficient n-octanol/ water	X	X	X	X
Flash point	X	X	X	X
Flammability	X	X	X	X
Explosive properties	X	X	X	X
Self-ignition temperature	X	X	X	X
Oxidising properties	X	X	X	X
Granulometry	X	X	X	X
Stability in organic solvents			X	X
Dissociation constant			X	X
Viscosity			X	X

*The annex only resumes the standard information required. For specific rules see Regulation (EC) No 1907/2006.

*Annex 2 Overview of the toxicological information required for registration depending on the quantity of substance manufactured or imported annually**

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Toxicological Information				
Skin irritation/Corrosion				
• Assessment human/animal data, acid/alkaline reserve	X	X	X	X
• In vitro skin irritation	X	X	X	X
• In vitro skin corrosion	X	X	X	X
• In vivo skin irritation		X	X	X
Eye irritation				
• Assessment human/animal data, acid/alkaline reserve	X	X	X	X
• In vitro eye irritation	X	X	X	X
• In vivo eye irritation		X	X	X
Skin sensitisation				
• Assessment human/animal data	X	X	X	X
• In vivo testing	X	X	X	X

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Toxicological Information				
Mutagenicity				
• In vitro mutagenicity test (bacteria)	X	X	X	X
• In vitro cytogenicity test (mammalian cells) or micronucleus test		X	X	X
• In vitro gen mutation test (mammalian cells)		X	X	X
Acute toxicity				
• By oral route	X	X	X	X
• By inhalation		X	X	X
• By dermal route		X	X	X
Repeated dose toxicity				
• Short-term toxicity study (28-day)		X	X	X
• Sub-chronic toxicity study (90-day)			X	X
Reproductive toxicity				
• Screening for reproductive/ developmental toxicity (OECD 421 or 422)		X	X	X
• Pre-natal developmental toxicity study			X	X
• Two-generation reproductive toxicity study			X	X
Toxicokinetics				
• Assessment of toxicokinetic behaviour		X	X	X
Carcinogenicity				
• Carcinogenicity study				X

*The annex only resumes the standard information required. For specific rules see Regulation (EC) No 1907/2006.

*Annex 3 Overview of the <u>ecotoxicological information</u> required for registration depending on the quantity of substance manufactured or imported annually**

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Ecotoxicological Information				
Aquatic toxicity				
• Short-term toxicity study on invertebrates	X	X	X	X
• Growth inhibition study on aquatic plants	X	X	X	X
• Short-term toxicity study on fishes		X	X	X
• Activated sludge respiration inhibition test		X	X	X
• Long-term toxicity study on invertebrates			X	X

Quantity of substance manufactured/imported	≥ 1 ton p.a.	≥ 10 tons p.a.	≥ 100 tons p.a.	≥ 1000 tons p.a.
Ecotoxicological Information				
• Long-term toxicity study on fishes				
• FELS toxicity test **or**			X	X
• Short-term toxicity on embryo and sac-fry-stages **or**			X	X
• Juvenile growth test			X	X
Degradation				
• Biotic				
• Ready biodegradability	X	X	X	X
• Simulation testing on ultimate degradation in surface water			X	X
• Soil simulation testing			X	X
• Sediment simulation testing			X	X
• Abiotic				
• Hydrolysis		X	X	X
• Identification of degradation products			X	X
Fate and behaviour in the environment				
• Adsorption/desorption screening		X	X	X
• Bioaccumulation in aquatic species			X	X
Effects on terrestrial organisms			X	X
• Short-term toxicity study on invertebrates			X	X
• Effects on soil micro-organisms			X	X
• Short-term toxicity study on plants			X	X
• Long-term toxicity study on invertebrates				X
• Long-term toxicity study on plants				X
Long-term toxicity study on sediment organisms				X
Long-term or reproductive toxicity study on birds				X

*The annex only resumes the standard information required. For specific rules see Regulation (EC) No 1907/2006.

Annex 4 Template for a substance inventory

Substance name	Alternative name (INN)	Trade name	Name of medicinal product	Listed in Annex IV / V	CAS	EINECS	Contact details contract manufacturer	Contact details supplier	MSDS	Remarks

Annex 5 Template for a questionnaire (developed at the Working Group REACH of the BAH)

Standardised REACH Questionnaire for the communication in the supply chain

Exchange of information concerning the preregistration / registration of substances according to Regulation (EC) 1907/2006

Concerning

☐ the substance _____ CAS-/ EINECS No. _____

☐ the substances (all substances)

contained in product _____ Supplier's Article No. _____

Customer No. _____

the downstream user

Company: _____ Street / Postal Code: _____

represented by: _____ Tel.-No.: _____

E-Mail-Address: _____ Fax-No.: _____

requests

for the application of this product

unmodified in a

☐ Medicinal Product: _____ t/a ☐ Foodstuff: _____ t/a

☐ Medical Device: _____ t/a ☐ Cosmetic: _____ t/a

or as a

☐ Starting material for synthesis (isolated intermediate product) _____ t/a

a declaration of intent as ☐ **Manufacturer,** ☐ **Importer** or ☐ **Supplier** of the above mentioned product to the following questions:

1. Will the substance(s) contained be preregistered? ☐ yes ☐ no
   If not, please give reasons:

2. Following preregistration, do you plan to register?
   ☐ yes, expected _____ [mm/yyyy]
   ☐ no
   If not, please give reasons:
   ☐ currently not to decide, Decision possible as from_____ [mm/yyyy]

3. If you do not plan to preregister/ register: Will the product still be available for the future? ☐ yes ☐ no
   Please give reasons:

Issued by:

Company: _____ Tel.-No. _____

E-Mail-Address: _____ Fax-No.: _____

Place: _____ Signature / Stamp: _____

Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Weinheim, den

_____

Dr. Ursula Tammler